

Ophthalmic Manifestations of HIV in the Highly Active Antiretroviral Therapy Era

L Mowatt^{1, 2}

ABSTRACT

HIV-related eye disease can be classified as retinal HIV microangiopathy, opportunistic infections, neuro-ophthalmic manifestations and unusual malignancies. There is a 52–100% lifetime accumulative risk of HIV patients developing eye problems. Seventy-seven per cent of patients with ocular manifestations of HIV had CD4 counts < 200 cells/ μ L. Cytomegalovirus (CMV) is the most prevalent opportunistic infection, however, Africa has a low incidence of this, and more commonly squamous cell carcinoma, compared to the western hemisphere. Due to highly active antiretroviral therapy (HAART), the anti-CMV therapy may be discontinued if the CD4⁺ T cell count is > 100 cells/ μ L for a minimum of three months. Despite HAART, patients with a CD4 count < 50 cells/ μ L have a similar risk of developing CMV retinitis as compared to the pre-HAART era. Opportunistic infections include CMV, herpetic retinopathy (progressive outer retinal necrosis – PORN), less commonly toxoplasmosis, pneumocystis and cryptococcus. Malignancies associated with HIV include Kaposi's sarcoma and conjunctival squamous cell carcinoma. Cranial nerve palsies, optic disc swelling and atrophy are characteristic neuro-ophthalmic features. They usually occur secondary to meningitis/encephalitis (from cryptococcus and tuberculosis). With the advent of HAART, new complications have developed in CMV retinitis: immune recovery uveitis (IRU) and cystoid macula oedema (CMO). Immune recovery uveitis occurs in 71% of patients if HAART is started before the induction of the anti-CMV treatment. However, this is reduced to 31% if HAART is started after the induction treatment. Molluscum contagiosum and Kaposi's sarcoma can spontaneously resolve on HAART. Highly active anti-retroviral therapy has reduced the frequencies of opportunistic infections and improved the remission duration in HIV patients.

Keywords: Cytomegalovirus retinitis, HAART, HIV, opportunistic infections

Manifestaciones Oftálmicas del VIH en la Era de la Terapia Antiretroviral Altamente Activa

L Mowatt^{1, 2}

RESUMEN

Las enfermedades oculares relacionadas con el VIH pueden clasificarse como microangiopatía retiniana por VIH, infecciones oportunistas, manifestaciones neuro-oftálmicas, y tumores inusuales. Hay un riesgo acumulativo de por vida de 52–100% de que los pacientes con VIH desarrollen problemas oculares. Setenta y siete por ciento de los pacientes con manifestaciones oculares por VIH tenían conteos de CD4 < 200 células/ μ L. El citomegalovirus (CMV) es la infección oportunista más frecuente. Sin embargo, África tiene una baja incidencia de CVM, siendo en cambio más común el carcinoma de células escamosas, en comparación con el hemisferio occidental. Debido a la terapia antiretroviral altamente activa (TAAA), la terapia anti-CMV puede suspenderse si el conteo de células CD4 + T es > 100 células/ μ L por un mínimo de tres meses. A pesar de la terapia TAAA, los pacientes con un conteo de CD4 < 50 células/ μ L tienen un riesgo similar de desarrollar retinitis por CMV en comparación con la era pre-TAAA. Las infecciones oportunistas incluyen CMV, retinopatía herpética (necrosis retiniana progresiva externa – PORN), y menos comúnmente toxoplasmosis, pneumocistosis, y cryptococcus. Los tumores malignos asociados con el VIH incluyen el sarcoma de Kaposi y el carcinoma de células escamosas de conjuntiva. La parálisis del nervio craneal, la inflamación del disco

From: ¹Department of Surgery, Radiology, Anaesthesia and Intensive Care, The University of the West Indies and ²University Hospital of the West Indies, Kingston 7, Jamaica, West Indies.

Correspondence: Dr L Mowatt, Department of Surgery, Radiology, Anaesthesia and Intensive Care, The University of the West Indies, Kingston 7, Jamaica, West Indies. E-mail: Lizettemowatt@yahoo.com

óptico, así como la atrofia, son características neuro-oftálmicas típicas. Generalmente se presentan de forma secundaria en los casos de meningitis, encefalitis (cryptococcus y tuberculosis). Con el advenimiento de TAAA, se han desarrollado nuevas complicaciones de la retinitis por CMV, a saber, la uveítis por recuperación inmunológica (IRU por su sigla en inglés) y el edema macular cistoide (EMC). La uveítis por recuperación inmunológica ocurre en 71% de los pacientes si la terapia TAAA se comienza antes de la inducción del tratamiento anti-CMV. Sin embargo, esta cantidad se reduce a un 31% si TAAA se inicia después del tratamiento de inducción. El molusco contagioso y el sarcoma de Kaposi pueden desaparecer espontáneamente con el TAAA. La terapia anti-retroviral altamente activa ha reducido las frecuencias de las infecciones oportunistas, y mejorado la duración de la remisión en pacientes con VIH.

Palabras claves: Retinitis por citomegalovirus, VIH, TAAA, infecciones oportunistas

West Indian Med J 2013; 62 (4): 306

INTRODUCTION

Ocular features of AIDS were first reported in 1983 (1). Through the early work of Holland and associates, the features of HIV retinopathy, opportunistic infections and Kaposi's sarcoma were first described (1–3). HIV patients have a 52–100% lifetime accumulative risk of getting ocular involvement (4). Seventy-seven per cent of patients with ocular manifestations of HIV had CD4 counts < 200 cells/ μ L (5, 6). The incidence and type of ophthalmic manifestations of HIV varies worldwide (5–11). The effect of HIV on the eye can be classified into retinal microangiopathy, opportunistic infections, neuro-ophthalmic problems and unusual malignancies [Table 1] (7–12).

19). In HAART-naïve patients, the odds ratio of HIV eye problems was 6.3 for CD4 count \leq 100 cells/ μ L and 1.3 for CD4 count 101–200 cells/ μ L. The CD4 count and WHO clinical stage are important predictors of the presence of HIV-related eye disease (19). The incidence of ocular complications since HAART is 26.3–50% (8, 20, 21). The role of the ophthalmologist cannot be underestimated in the management of HIV patients.

Retinal microangiopathy

HIV retinal microangiopathy is characterized by intraretinal haemorrhages with cotton wool spots (white ill-defined retinal lesions indicating retinal ischaemia), but does not cause

Table: Main ocular manifestations of HIV/AIDS

Opportunistic infections	Neuro-ophthalmic manifestations	Unusual malignancies	Retinal vasculopathy	Ocular complications
Cytomegalovirus	Extra ocular motility disorders	Squamous cell carcinoma	HIV microangiopathy:	Immune recovery uveitis (IRU)
Herpetic (PORN)	Optic disc swelling	Kaposi's sarcoma	Intraretinal haemorrhages	Retinal detachment
Toxoplasmosis	Optic atrophy	Primary ocular lymphoma	Cotton wool spots	Cataract
Pneumocystis	Visual field defects			Macula oedema
Syphilis	secondary to			
Mycobacteria	cryptococcal,			
Cryptosporidium	tuberculous, syphilitic			
Microsporidia	meningitis,			
	Central nervous system			
	toxoplasmosis and			
	lymphoma			

Highly active antiretroviral therapy (HAART) consists of combination therapy: two nucleoside reverse transcriptase inhibitors and a protease inhibitor which result in substantial and sustained suppression of the HIV replication [HIV RNA viral load] (13). Highly active antiretroviral therapy has been successful in decreasing the mortality and morbidity of HIV patients (14–16). With the patient's immune recovery and increase in CD4 counts, opportunistic infections have a reduced frequency and less aggressive course (17, 18).

The odds ratio of developing eye problems in HIV patients with World Health Organization (WHO) clinical stage 3–4 was 9.4, compared to 1 for those with stage 1–2 (5,

visual problems (Fig. 1). Most HIV patients are referred for an eye examination when they have visual problems, therefore, the true incidence of HIV retinopathy may be underestimated. HIV retinal microangiopathy is significantly associated with mortality [$p = 0.005$] (22).

Opportunistic infections

Cytomegalovirus (CMV) retinitis is the most prevalent opportunistic infection occurring in AIDS patients (7, 8, 12, 23). Approximately 30% of patients with AIDS developed CMV retinitis before HAART (16, 24). The estimated lifetime cumulative incidence of CMV retinitis is 25–40% (7).



Fig. 1: Cotton wool spots in HIV retinal microangiopathy.

Hodge *et al* looked at over 5200 person years of follow-up in HIV patients *versus* 30 100 person years of follow-up in non-HIV patients to determine the incident relative risk of opportunistic infections in San Francisco (7). They found 790 cases of CMV retinitis amongst the HIV group and none in the non-HIV group, making the relative risk incidence of CMV retinitis infinite in the HIV group. The relative risk incidence of pneumocystis choroidopathy and ocular syphilis was also infinite, but the risk was much lower than that of CMV (7).

The relative risk of herpes zoster, fungal retinitis, toxoplasmosis retinitis and herpes simplex was 6.6:1, 4.9:1, 2.1:1 and 1.2:1, respectively (7). The incidence of toxoplasmosis retino-choroiditis (11%), herpetic retinopathy (1–3%), *Pneumocystis jirovecii*, tuberculous and cryptococcus choroiditis, syphilitic retinitis, and intraocular lymphoma is infrequent (21, 25). Even in the HAART era, fluconazole maintenance therapy is recommended (200 mg/day) in all patients who have had cryptococcus infection (20).

Cytomegalovirus retinitis

The worldwide incidence of CMV retinitis (except in Africa) is 18–40% (21, 25). The incidence of CMV retinitis in Africa is lower, 0–16.5%; however, anterior segment findings: herpes zoster ophthalmicus (HZO) and squamous cell carcinoma (SCC), are more common there (5, 6, 26–28). This may result from differences in race, HIV subtypes, comorbidity or early mortality from systemic opportunistic diseases before the CD4 count falls low enough for the opportunistic infections to occur (5, 27).

Cytomegalovirus enters the eye through the retinal blood vessels and is found in the vascular endothelial cells at the edge of the lesion. It causes full thickness retinal necrosis with associated haemorrhage (haemorrhagic retinitis otherwise called ‘pizza pie’ appearance) which spreads in a contiguous manner. It may uncommonly have an indolent progression with granular lesions in the peripheral retina.

Symptoms include floaters, visual field defects or visual loss, with macula involvement or retinal detachment [RD] (29). Retinal detachment occurs in 13–29% of patients, usually in the healing phase, and requires pars plana vitrectomy, endolaser and intraocular silicone oil to tamponade the retina (20). Since the advent of HAART, RDs have reduced by 60–80% (20, 25). The risk factors for developing RDs included a lower CD4 T cell count and larger CMV retinitis lesions (30). In the pre HAART era, the rate of RD in a CMV retinitis patient was ~0.50/person years, but this has been decreased in the HAART era to 0.06/person years (30). Second eye or contralateral involvement occurred *via* the haematogenous route and was a more frequent occurrence in the pre HAART era. For patients who were treated with an intravitreal injection of anti-CMV medication, their rate of contralateral eye disease was 0.1/person year. This was reduced to 0.05/person year if they received systemic anti-CMV drugs (30).

Cytomegalovirus produces cytokine homologues, *eg* interleukin 10, which inhibits T helper type-1 (Th1), a key to cell mediated immunity. It also produces chemokine receptors, which inhibit inflammatory and immune cells by binding chemokine, which can accelerate the time from HIV to AIDS (31, 32).

In the pre HAART era, the odds ratio for developing CMV retinitis in patients with baseline CD4⁺ lymphocyte counts of 0–50 cells/ μ L was 4.6 ($p = 0.002$) compared with patients with CD4⁺ lymphocyte counts of 101–250 cells/ μ L (33). Hamamotoo *et al* showed the average CD4⁺ T-cell counts at diagnosis of CMV retinitis were 45.2/ μ L before and 116.7/ μ L after HAART (34). Having a CD4⁺ T cell count < 50 cells/ μ L was the single most important risk factor ($p < 0.0001$) for developing retinitis (35). In the present HAART era, the incidence of CMV retinitis in patients with AIDS is 0.36/100 person years (35). Despite HAART, patients with < 50 CD4 T-cells/ μ L have a similar risk of developing CMV retinitis as compared to the pre HAART era (36). Complications of CMV retinitis occurs in 39% of patients and include RD, uveitis and optic atrophy, however, immune recovery uveitis (IRU) and cystoid macula oedema (CMO) are only seen in patients receiving HAART (23).

Cytomegalovirus treatment

Cytomegalovirus retinitis is treated with ganciclovir (intravenous or intravitreal implant) or oral valganciclovir, which has a very high oral bioavailability and good safety profile. Oral ganciclovir should not be used as it has 1/10 the bioavailability of oral valganciclovir. The pre HAART era required patients to have lifetime maintenance of these drugs, which have a risk of granulocytopenia, anaemia and thrombocytopenia. Selective discontinuation of anti-CMV treatment may be considered in HAART patients if the CD4⁺ T cell count is > 100 cells/ μ L for a minimum of three months or a 2-log unit or greater decrease in the HIV viral load (37). Deayton *et al* showed no CMV retinitis progression after six months of treatment in HAART patients over an eight-year

period (23). A second line option includes foscarnet and cidofovir, however, these drugs can have severe side effects, including nephrotoxicity.

Cytomegalovirus remission duration

Patients who received HAART had a median CMV retinitis remission duration of 574 days, whereas those not on HAART had a median remission of 80.5 days [$p < 0.001$] (70). The reduction in the viral load ($p = 0.007$) was a better clinical predictor for CMV retinitis remission *versus* the CD4 count [$p = 0.058$] (38).

Herpetic necrotizing retinopathy

The herpes virus, varicella zoster, causes two clinical types of posterior segment inflammation: acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN). Acute retinal necrosis occurs in immunocompetent and AIDS patients with $CD4 < 100$ cells/ μ L, but PORN occurs only in severely immunocompromised patients (21). Treatment of ARN is with intravenous acyclovir for one week then oral acyclovir for six weeks, or oral valacyclovir. Prophylactic laser photocoagulation would be required to prevent a retinal detachment. Progressive outer retinal necrosis is a very aggressive retinitis which results in $> 30\%$ of patients going blind, and requires intravitreal ganciclovir injections and intravenous treatment (39, 40).

Immune recovery uveitis

Immune recovery uveitis (IRU) is part of the immune recovery inflammatory syndrome (IRIS) which is associated with immune reconstitution in organs with opportunistic infections such as mycobacteria, CMV, cryptococcal, toxoplasmosis and *Pneumocystis jirovecii* pneumonia (41). Patients develop IRIS within four to eight weeks of starting HAART and have high viral loads and low CD4 T lymphocyte count. Due to immune reconstitution on HAART, patients have a stronger immunological response to infections, resulting in inflammation (uveitis or vitritis) which is deleterious to the eye. The diagnosis may be equivocal, as it must be differentiated from progression of the infection, antimicrobial resistance, treatment failure, organ dysfunction or drug toxicity (41, 42).

Immune recovery uveitis did not occur prior to HAART and has had increasing incidence since its implementation (34). Immune recovery uveitis occurs in 0.12–0.8 cases per person year (42). It is seen in 14–16.9% of patients recovering from CMV retinitis, resulting in CMO, a cause of visual loss amongst IRU patients (8, 43–45). Cidofovir, an acyclic nucleotide analogue used in the treatment of CMV, had a 3.3 times greater risk of developing IRU *versus* an alternative treatment [$p = 0.4$] (46). Treatment is with corticosteroids and discontinuing the drug.

The timing of commencing HAART in patients with active CMV retinitis is important to their clinical progress (47). If HAART is started before the two-week induction of

CMV therapy is completed, 71% of patients develop an IRU. However, if started after induction and suppression of retinitis, the incidence of IRU reduces to 31% (47). However, this is specific to CMV, as the vitritis can cause serious problems such as further retinal necrosis, RD, cataract and glaucoma. Zolopa *et al* proved that early commencement of antiretroviral therapy for opportunistic infections such as *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis and bacterial infections results in fewer AIDS progression and death (37).

Other infections

In an African study, 96% of patients with tuberculosis (TB) presenting to a hospital with fever had HIV; of these, 2.8% had choroidal granulomas (27). In Southeast Asia, the prevalence of *Toxoplasma gondii* antibody is similar in HIV-positive (23.2%) *versus* HIV-negative patients [29.5%] (48). Brazil has a high incidence of ocular toxoplasmosis occurring in 8.5% of patients, whereas CMV retinitis is seen in 25% of cases (49). Toxoplasma is more likely to present as toxoplasma encephalitis than ocular disease (50). The incidence of the opportunistic infections and ocular signs vary geographically.

Molluscum contagiosum, discrete, elevated, pearly white umbilicated lesions of the eyelids can be a presenting ocular feature of HIV disease (50). It occurs in 1% of HIV patients, with extensive dissemination and an aggressive course compared to its normal appearance (9, 51). Treatment options include incision and curettage, liquid nitrogen, trichloroacetic acid or cryotherapy. However, patients on HAART may undergo spontaneous resolution of *Molluscum contagiosum* within six months (52, 53).

Microsporidia, an obligate intracellular protozoan parasite was first reported in an HIV-positive patient in 1985 (54). Prior to this, only 10 cases had been reported in humans, but in the first decade of the HIV epidemic there were more than 400 reported cases in HIV patients (55). It presents as keratoconjunctivitis and is diagnosed by conjunctival scraping or biopsy. Commencement on HAART has been shown to lead to resolution of the keratoconjunctivitis (56).

Ocular inflammation secondary to drugs

Rifabutin is a rifamycin derivative used for treatment and prophylaxis against *Mycobacteria avium* complex (MAC) infections in HIV patients (42). At doses of 300–1800 gm/day, it may cause a unilateral or bilateral anterior uveitis, vitritis and retinal vasculitis which is dose related. The severity may result in a hypopyon (pus in the anterior chamber of the eye), two to seven months after initiating treatment (42, 57–60). The risk increases with concurrent use of protease inhibitors (part of HAART); the mechanism of action is unknown and treatment may be with corticosteroids, reducing or discontinuing the drug (42, 57–59). Rifabutin may also cause stellate corneal endothelial deposits

in 18% of patients (61). It is important that pulmonologists and ophthalmologists are aware of the induced uveitis, so that patients are referred early for management.

Neuro-ophthalmic features

Neuro-ophthalmic manifestations may involve the afferent and extraocular pathways, resulting in visual loss, visual field defects or extraocular motility disorders. Neuro-ophthalmic problems may occur in up to 50% of HIV patients with 75–90% of patients having histologic evidence of brain or optic nerve involvement (62, 63).

Optic neuropathy occurs in HIV due to an infectious, compressive, inflammatory or infiltrative process. The HIV DNA is more commonly found in the optic nerve than retina (4:1), and the resulting degenerative change is secondary to HIV infected macrophages instead of direct viral infection (63). Visual evoked potential (VEP) was reduced in 57% and 42% of patients with and without neurological dysfunction, which supports the hypothesis of axonal loss occurring in HIV positive patients regardless of neurological symptoms (62). Patients may present with sub-acute bilateral painless optic neuropathy, for which antiretrovirals and corticosteroids are of no benefit, as it is due to microvascular ischaemia of the optic nerve head (64). This can lead to optic atrophy (Fig. 2). *Cryptococcus neoformans* is the most likely cause

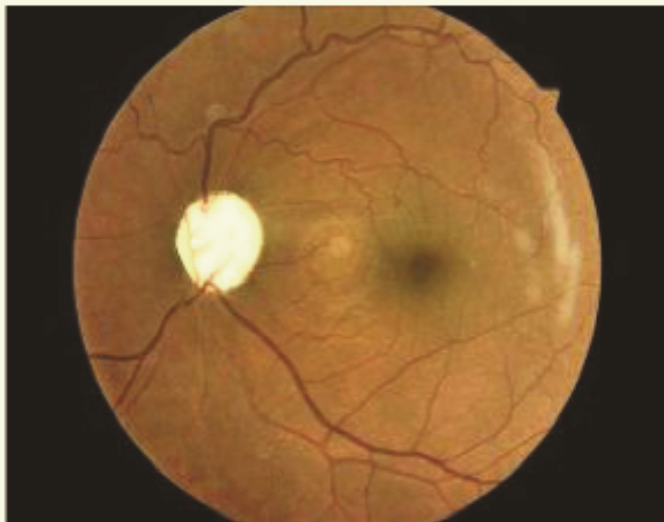


Fig. 2: Optic atrophy.

of optic disc swelling and may be associated with meningitis (65). With the use of HAART, IRIS may occur and 50% may lose vision because of raised intracranial pressure (65).

Eighty-six per cent of patients with neuro-ophthalmic disorders in AIDS have extra ocular motility disorders; palsies of the 3rd and 6th nerve, being most common, are usually secondary to toxoplasmosis and cryptococcosis meningitis (62). The prevalence of toxoplasma encephalitis has reduced with HAART, from 5.7% to 2.2% [$p = 0.015$] (66). Homonymous hemianopia can be a presenting sign of HIV,

due to a cerebral abscess secondary to TB or opportunistic infection associated meningitis (67).

Unusual malignancies

Oculocutaneous Kaposi's sarcoma (KS), an AIDS defining disease, may occur in the conjunctiva or eyelids as a flat or elevated bluish purple lesion (2, 42). It occurs in 9% of HIV patients and may be mistaken for a subconjunctival haemorrhage, pyogenic granuloma or lymphangioma (42, 68). Ocular KS may be treated if eyelid function is affected or for cosmesis (42). The treatment options include radiation, excision, cryotherapy, chemotherapy (bleomycin, doxorubicin, vinblastine) or subconjunctival interferon alpha2a; however, recurrence and progression can occur despite treatment (42, 69). With HAART, the treatment results vary. In Italy, there was 91% remission with HAART treatment, with complete remission occurring over five years, associated with significant CD4 cell count increase and decrease in HIV-1 RNA copies (70). Dupoint *et al*, in a Paris study, noted complete remission in 52.6% patients on HAART, even without specific KS treatment; this may be due to improvement in the immune status (71).

Squamous cell carcinoma (SCC) is seen mainly in sub-Saharan Africa, occurring in 3.8–7.8% of HIV patients. It presents at an earlier age and is more aggressive in HIV patients (72). Squamous cell carcinoma was the initial manifestation of HIV in 79% of patients in Malawi (73). It is uncommon in Europe and Australia (74). Squamous cell carcinoma typically occurs on the eyelids or conjunctiva, where it may be mistaken for a pterygium. It has been seen in the Jamaican population. The male to female ratio is 1.7:1 with a mean age of 40 years (26). Squamous cell carcinoma of the conjunctiva can be aggressive, requiring enucleation or exenteration (removal of the eye and all the orbital contents) or it may be treated with topical interferon alpha2b to prevent recurrence (75). Highly active antiretroviral therapy has not shown a reduction of incidence in AIDS defining head and neck cancers (74, 76).

Non-Hodgkin's lymphoma is the second most common opportunistic neoplasm in HIV infection, accounting for 3.5–5% of AIDS defining illnesses patients. Ocular involvement may occur in the adnexae with eyelid masses or infiltrate the orbit resulting in a painful proptosis. Primary intraocular lymphoma (PIL) is rare (7). Typically intraocular lymphoma presents as a unilateral or bilateral vitritis unresponsive to corticosteroids. Vitreous biopsy is essential for diagnosis. Since HAART, the incidence of Non-Hodgkin's lymphoma in HIV patients has reduced, but the effect on PIL has not been studied. There has been a case report of an HIV-positive patient who presented with an intraocular B cell lymphoma (CD4 count of 44 cells/ μ L) in a blind eye, and was treated with radiotherapy and chemotherapy. However, three years later he represented with a conjunctival SCC in the same eye; the HIV patient is at risk of multiple cancers (77).

Causes of visual loss in HIV patients

In the pre HAART era, maculopathy (from extension of CMV retinitis) was the primary cause for visual loss of 20/200 or worse ($\leq 20/200$) in 84% of AIDS patients, with RD being the second most common cause [36–63%] (29). In the post HAART era, it still remains the leading cause in 69.8% of cases. However, in the HAART era, cataract has become the second most common cause of visual loss, occurring in 28.6%; retinal detachment is third at 16.7% and macula oedema, which was $< 5\%$ pre HAART, is now the fourth most common cause of visual loss in 11.1% of cases (29). In the Studies of the Ocular Complications of AIDS (SOCA), they assessed the ocular examination of patients at the time of diagnosis and found that cataract was more common in HIV/AIDS patients compared to age-matched norms (78). However, RD still gives the highest risk of visual loss with 42% of patients developing legal blindness ($> 20/200$) despite surgery. Cataract on the other hand, is a cause of reversible blindness.

CONCLUSION

Highly active antiretroviral therapy has reduced the incidence of opportunistic infections, increased the time of remission, reduced the complications of CMV and has allowed the discontinuation of anti-CMV medications and the spontaneous regression of Kaposi's sarcoma. It has changed the face of HIV-related eye disease with respect to new complications with CMV as with immune recovery uveitis, cystoid macula oedema and cataract. Blepharitis and keratoconjunctivitis are now the commonest ocular features of HIV in the HAART era in Brazil, but cytomegalovirus remains the most prevalent OI (11).

In the Caribbean, there is a reported 54.8–70.1% adherence to taking antiretroviral therapy and a 6% resistance to the drug therapy (79, 80). In Jamaica, 4.7% of patients have opportunistic infections and we have shown an improvement in CD4 count with antiretroviral therapy, but studies are yet to be done to look at the reduction of ocular morbidity with HAART in the West Indies (81, 82).

REFERENCES

- Holland GN, Gottlieb MS, Schanker HM, Pettit TH. Ocular disorders associated with a new severe acquired cellular immunodeficiency syndrome. *Am J Ophthalmol* 1982; **93**: 393–402.
- Holland GN, Pepose JS, Pettit TH, Gottlieb MS, Yee RD, Foos RY. Acquired immune deficiency syndrome. Ocular manifestations. *Ophthalmology* 1983; **90**: 859–73.
- Holland GN, Gottlieb MS, Foos RY. Retinal cotton-wool patches in acquired immunodeficiency syndrome. *N Engl J Med* 1982; **307**: 1704.
- Biswas J, Madhavan HN, George AE, Kumarasmy N, Solomon S. Ocular lesions associated with HIV infection in India: a series of 100 consecutive patients evaluated at a referral centre. *Am J Ophthalmol* 2000; **129**: 9–15.
- Pathai S, Deshpande A, Gilbert C, Lawn S. Prevalence of HIV-associated ocular disease among patients enrolling for antiretroviral treatment in India: a cross-sectional study. *BMC Infect Dis* 2009; **9**: 158. E-pub 2009 September 23. doi: 10.1186/1471-2334-9-158.
- Sahoo S. HIV- and AIDS-related ocular manifestations in Tanzanian patients. *Malays J Med Sci* 2010; **17**: 12–6.
- Hodge WG, Seiff SR, Margolis TP. Ocular opportunistic infection incidences among patients who are HIV positive compared to patients who are HIV negative. *Ophthalmology* 1998; **105**: 895–900.
- Wang Z, Jia R, Ge S, He T, Zhang Y, Yang Y et al. Ocular complications of human immunodeficiency virus infection in Eastern China. *Am J Ophthalmol* 2012; **153**: 363–9.
- Kim SJ, Park SJ, Yu HG, Kim NJ, Jang HC, Oh MD. Ocular manifestations of acquired immunodeficiency syndrome in Korea. *Korean Med Sci* 2012; **27**: 542–6.
- Belfort R, Muccioli C. Experience of HIV/AIDS and the eye in Brazil, South America. *Community Eye Health* 1995; **8**: 26–7.
- Rodrigues ML, Rodrigues M de L, Figueiredo JF, de Freitas JA. Ocular problems in Brazilian patients with AIDS before and in highly active antiretroviral therapy (HAART) era. *Braz J Infect Dis* 2007; **11**: 199–202.
- Vrabec TR. Posterior segment manifestations of HIV/AIDS. *Surv Ophthalmol* 2004; **49**: 131–57.
- Hammer SM, Eron JJ Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society – USA panel. *JAMA* 2008; **300**: 555–70. doi: 10.1001/jama.300.5.555.
- Grabar S, Le Moing V, Goujard C, Leport C, Kazatchkine MD, Costagliola D et al. Clinical outcomes of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. *Ann Intern Med* 2000; **133**: 401–10.
- Murphy EL, Collier AC, Kalish LA, Assmann SF, Para MF, Flanigan TP et al. Highly active antiretroviral therapy decreases mortality and morbidity in patient with advanced HIV disease. *Ann Intern Med* 2001; **135**: 17–26.
- Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; **338**: 853–60.
- Doan S, Cochereau I, Guvenisik N, Diraison MC, Mousalatti H, Thanh HX. Cytomegalovirus retinitis in HIV infected patients with and without highly active antiretroviral therapy. *Am J Ophthalmol* 1999; **128**: 250–1.
- Macdonald JC, Karavellas MP, Torriani FJ, Morse LS, Smith IL, Reed JB et al. Highly active antiretroviral therapy-related immune recovery in AIDS patients with cytomegalovirus retinitis. *Ophthalmology* 2000; **107**: 877–83.
- World Health Organization. Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance. African region. 2005 [cited 2012 Dec 27]. Available from: <http://www.who.int/hiv/pub/guidelines/clinicalstaging.pdf>
- Banker AS. Posterior segment manifestations of human immunodeficiency virus/acquired immune deficiency syndrome. *Indian J Ophthalmol* 2008; **56**: 377–83.
- Arruda RF, Muccioli C, Belfort R Jr. Ophthalmological findings in HIV infected patients in the post-HAART (highly active anti-retroviral therapy) era, compared to the pre-HAART era. *Rev Assoc Med Bras* 2004; **50**: 148–52.
- Lai TY, Wong RL, Luk FO, Chow VW, Chan CK, Lam DS. Ophthalmic manifestations and risk factors for mortality of HIV patients in the post-highly active anti-retroviral therapy era. *Clin Experiment Ophthalmol* 2011; **39**: 99–104.
- Deayton JR, Wilson P, Sabin CA, Davey CC, Johnson MA, Emery VC et al. Changes in the natural history of cytomegalovirus disease following the introduction of highly active antiretroviral therapy. *AIDS* 2000; **14**: 1163–70.
- Varani S, Spezzacatena P, Manfredi R, Chiodo F, Mastroianni A, Ballarini P et al. The incidence of cytomegalovirus (CMV) antigenemia and CMV disease is reduced by highly active antiretroviral therapy. *Eur J Epidemiol* 2000; **16**: 433–7.
- Goldberg DE, Smith LM, Angelilli A, Freeman WR. HIV-associated retinopathy in the HAART era. *Retina* 2005; **25**: 633–49.
- Onakoya AO, Odeyemi MG, Aribaba OT, Akinsola FB. Ocular findings in acquired immunodeficiency syndrome patients in Lagos, Nigeria. *Nig Q J Hosp Med* 2012; **22**: 52–7.

27. Beare NAV, Kublin JG, Lewis DK, Schijffelen MJ, Peters RPH, Joaki G et al. Ocular disease in patients with tuberculosis and HIV presenting with fever in Africa. *Br J Ophthalmol* 2002; **86**: 1076–9.
28. Nkomazana O, Tshitswana D. Ocular complications of HIV infection in sub-Saharan Africa. *Curr HIV/AIDS Rep* 2008; **5**: 120.
29. Thorne JE, Jabs DA, Kempen JH, Holbrook JT, Nichols C, Meinert CL et al. Causes of visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Ophthalmology* 2006; **113**: 1441–5.
30. Jabs DA, Van Natta ML, Thorne JE, Weinberg DV, Meredith TA, Kuppermann BD et al. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 2. Second eye involvement and retinal detachment. *Ophthalmology* 2004; **111**: 2232–9.
30. Jabs DA. Cytomegalovirus retinitis and the acquired immunodeficiency syndrome – bench to bedside: LXVII Edward Jackson Memorial Lecture. *Am J Ophthalmol* 2011; **151**: 198–216.
31. Sabin CA, Phillips AN, Lee CA, Janossy G, Emery V, Griffiths PD. The effect of CMV infection on progression of human immunodeficiency virus disease is a cohort of haemophilic men followed for up to 13 years from seroconversion. *Epidemiol Infect* 1995; **114**: 361–72.
32. Pertel P, Hirschtick R, Phair J, Chmiel J, Poggensee L, Murphy R. Risk of developing cytomegalovirus retinitis in persons infected with the human immunodeficiency virus. *J Acquir Immune Defic Syndr* 1992; **5**: 1069–74.
33. Hamamotoo A, Tatebayashi M, Uehira A, Kuroda S, Morimoto Y, Nakagawa T et al. Retrospective study of ocular complications in patients with human immunodeficiency virus infection before and after HAART. *Nihon Ganka Gakkai Zasshi* 2012; **116**: 721–9.
34. Sugar EA, Jabs DA, Ahuja A, Thorne JE, Danis RP, Meinert CL et al. Incidence of cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol* 2012; **153**: 1016–24.
35. Butler NJ, Thorne JE. Status of HIV infection and ocular disease. *Curr Opin Ophthalmol* 2012; **23**: 517–22.
36. Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One* 2009; **4**: e5575.
37. Lin DY, Warren JF, Lazzaroni LC, Wolitz RA, Mansour SE. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy in HIV infected patients: natural history and clinical predictors. *Retina* 2002; **22**: 268–77.
38. Yin PD, Kurup SK, Fischer SH, Rhee HH, Byrnes GA, Levy-Clarke GA et al. Progressive outer retinal necrosis in the era of highly active antiretroviral therapy: successful management with intravitreal injections and monitoring with quantitative PCR. *J Clin Virol* 2007; **38**: 254–9.
39. Gore DM, Gore SK, Visser L. Progressive outer retinal necrosis: outcomes in the intravitreal era. *Arch Ophthalmol* 2012; **130**: 700–6.
40. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009; **58**: 1–207.
41. Jeng BH, Holland GN, Lowder CY, Deegan WF 3rd, Raizman MB, Meisler DM. Anterior segment and external ocular disorders associated with human immunodeficiency virus disease. *Surv Ophthalmol* 2007; **52**: 329–68.
42. Alp MN, Baykam N, Kural G. Immune recovery uveitis associated with highly active antiretroviral therapy in a patient with CMV retinitis and AIDS despite a low CD4+ T cell count: case report and a review of the literature. *Int Ophthalmol* 2010; **30**: 183–9.
43. Guzak R, Rodman J, Pizzimenti J. Cystoid macular edema as a result of immune-recovery uveitis. *Optom Vis Sci* 2011; **88**: E344–51.
44. Kempen JH, Min YI, Freeman WR, Holland GN, Friedberg DN, Dieterich DT et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Ophthalmology* 2006; **113**: 684–94.
45. Song MK, Azen SP, Buley A, Torriani F, Cheng L, Chaidhawangul S et al. Effect of anti-cytomegalovirus therapy on the incidence of immune recovery uveitis in AIDS patients with healed cytomegalovirus retinitis. *Am J Ophthalmol* 2003; **136**: 696–702.
46. Ortega-Larrocea G, Espinosa E, Reyes-Terán G. Lower incidence and severity of cytomegalovirus-associated immune recovery uveitis in HIV-infected patients with delayed highly active antiretroviral therapy. *AIDS* 2005; **19**: 735–8.
47. Sukthana Y, Chintana T, Lekklā A. Toxoplasma gondii antibody in HIV infected persons. *J Med Assoc Thai* 2000; **83**: 681–4.
48. Hoffmann C, Ernst M, Meyer P, Wolf E, Rosenkranz T, Plettenberg A et al. Evolving characteristics of toxoplasmosis in patients infected with human immunodeficiency virus-1: clinical course and Toxoplasma gondii-specific immune responses. *Clin Microbiol Infect* 2007; **13**: 510–5.
49. Leahey AB, Shane JJ, Listhaus A, Trachtman M. Molluscum contagiosum eyelid lesions as the initial manifestation of acquired immunodeficiency syndrome. *Am J Ophthalmol* 1997; **124**: 240–1.
50. Robinson MR, Udell IJ, Garber PF, Perry HD, Streeten BW. Molluscum contagiosum of the eyelids in patients with acquired immune deficiency syndrome. *Ophthalmology* 1992; **99**: 1745–7.
51. Calista D, Boschini A, Landi G. Resolution of disseminated Molluscum contagiosum with highly active anti-retroviral therapy (HAART) in patients with AIDS. *Eur J Dermatol* 1999; **9**: 211–3.
52. Schulz D, Sarra GM, Koerner UB, Garweg JG. Evolution of HIV-1-related conjunctival Molluscum contagiosum under HAART: report of a bilaterally manifesting case and literature review. *Graefes Arch Clin Exp Ophthalmol* 2004; **242**: 951–5.
53. Modigliani R, Bories C, Le Charpentier Y, Salmeron M, Messing B, Galian A et al. Diarrhoea and malabsorption in acquired immune deficiency syndrome: a study of four cases with special emphasis on opportunistic protozoan infestations. *Gut* 1985; **26**: 179–87.
54. Bryan RT. Microsporidiosis as an AIDS-related opportunistic infection. *Clin Infect Dis* 1995; **21** (Suppl): 62–5.
55. Martins SA, Muccioli C, Belfort R Jr, Castelo A. Resolution of microsporidial keratoconjunctivitis in an AIDS patient treated with highly active antiretroviral therapy. *Am J Ophthalmol* 2001; **131**: 378–9.
56. Bazewicz M, Fikri J, Martin CH, Libois A, Meunier A, Frippiat F et al. Drug-induced uveitis in AIDS patients: two case reports. *Bull Soc Belge Ophtalmol* 2011; **318**: 19–23.
57. Ishiguchi N, Ueno K, Yanagihara M, Kadono K, Oshika T. Rifabutin-associated hypopyon uveitis in patient with acquired immunodeficiency syndrome. *Nihon Ganka Gakkai Zasshi* 2010; **114**: 683–6.
58. Wang HH, Chung YM, Lin YC, Hu HC, Wong WW. Rifabutin-induced hypopyon uveitis in patients with acquired immunodeficiency syndrome infected with Mycobacterium avium complex. *J Chin Med Assoc* 2007; **70**: 136–9.
59. Arevalo JF, Russack V, Freeman WR. New ophthalmic manifestations of presumed rifabutin-related uveitis. *Ophthalmic Surg Lasers* 1997; **28**: 321–4.
60. Smith JA, Mueller BU, Nussenblatt RB, Whitcup SM. Corneal endothelial deposits in children positive for human immunodeficiency virus receiving rifabutin prophylaxis for Mycobacterium avium complex bacteremia. *Am J Ophthalmol* 1999; **127**: 164–9.
61. Mwanza JC, Nyamabo LK, Tylleskär T, Plant GT. Neuro-ophthalmological disorders in HIV infected subjects with neurological manifestations. *Br J Ophthalmol* 2004; **88**: 1455–9.
62. Sadun AA, Pepose JS, Madigan MC, Laycock KA, Tenhula WN, Freeman WR. AIDS-related optic neuropathy: a histological, virological and ultrastructural study. *Graefes Arch Clin Exp Ophthalmol* 1995; **233**: 387–98.
63. Laurent-Coriat C, Tilikete C, Bouhour D, Boulliat J, Fleury J, Bernard M et al. HIV infection presenting with bilateral optic neuropathy. *Rev Neurol (Paris)* 2006; **162**: 95–7.
64. Khurana RN, Javaheri M, Rao N. Ophthalmic manifestations of immune reconstitution inflammatory syndrome associated with Cryptococcus neoformans. *Ocul Immunol Inflamm* 2008; **16**: 185–90.

65. Maschke M, Kastrup O, Esser S, Ross B, Hengge U, Hufnagel A. Incidence and prevalence of neurological disorders associated with HIV since the introduction of highly active antiretroviral therapy (HAART). *J Neurol Neurosurg Psychiatry* 2000; **69**: 376–80.
66. Gharai S, Venkatesh P, Sinha A, Garg S, Ghosh P. Isolated homonymous hemianopsia due to presumptive cerebral tubercular abscess as the initial manifestation of human immunodeficiency virus infection. *Indian J Ophthalmol* 2012; **60**: 321–4.
67. Pepose JS, Holland GN, Nestor MS, Cochran AJ, Foos RY. Acquired immune deficiency syndrome; pathogenic mechanisms of ocular disease. *Ophthalmology* 1985; **92**: 472–84.
68. Shuler JD, Holland GN, Miles SA, Miller BJ, Grossman I. Kaposi sarcoma of the conjunctiva and eyelids associated with the acquired immunodeficiency syndrome. *Arch Ophthalmol* 1989; **107**: 858–62.
69. Cattelan AM, Calabrò ML, De Rossi A, Aversa SM, Barbierato M, Trevenzoli M et al. Long-term clinical outcome of AIDS-related Kaposi's sarcoma during highly active antiretroviral therapy. *Int J Oncol* 2005; **27**: 779–85.
70. Dupont C, Vasseur E, Beauchet A, Aegerter P, Berthé H, de Truchis P et al. Long-term efficacy on Kaposi's sarcoma of highly active antiretroviral therapy in a cohort of HIV-positive patients. *CISIH 92. Centre d'information et de soins de l'immunodéficience humaine. AIDS* 2000; **14**: 987–93.
71. Nagaiah G, Stotler C, Orem J, Mwanda WO, Remick SC. Ocular surface squamous neoplasia in patients with HIV infection in sub-Saharan Africa. *Curr Opin Oncol* 2010; **22**: 437–42.
72. Spitzer MS, Batumba NH, Chirambo T, Bartz-Schmidt KU, Kayange P, Kalua K et al. Ocular surface squamous neoplasia as the first apparent manifestation of HIV infection in Malawi. *Clin Experiment Ophthalmol* 2008; **36**: 422–5.
73. Purgina B, Pantanowitz L, Seethala RR. A review of carcinomas arising in the head and neck region in HIV-positive patients. *Patholog Res Int* 2011; **2011**: 469150. doi: 10.4061/2011/469150. Epub 2011 May 10.
74. Shields CL, Ramasubramanian A, Mellen PL, Shields JA. Conjunctival squamous cell carcinoma arising in immunosuppressed patients (organ transplant, human immunodeficiency virus infection). *Ophthalmology* 2011; **118**: 2133–7.
75. Cheung MC, Pantanowitz L, Dezube BJ. AIDS-related malignancies: emerging challenges in the era of highly active antiretroviral therapy. *Oncologist* 2005; **10**: 412–26.
76. Babu K, Murthy KR, Krishnakumar S. Two successive ocular malignancies in the same eye of a HIV-positive patient: a case report. *Ocul Immunol Inflamm* 2010; **18**: 101–3.
77. Jabs DA, Van Natta ML, Holbrook JT, Kempen JH, Meinert CL, Davis MD et al. Longitudinal study of the ocular complications of AIDS: 2. Ocular examination results at enrollment. *Ophthalmology* 2007; **114**: 787–93.
78. Allen CF, Simon Y, Edwards J, Simeon DT. Adherence to antiretroviral therapy by people accessing services from non-governmental HIV support organizations in three Caribbean countries. *West Indian Med J* 2011; **60**: 269–75.
79. Harvey KM, Carrington D, Duncan J, Figueroa JP, Hirschorn L, Manning D et al. Evaluation of adherence to highly active antiretroviral therapy in adults in Jamaica. *West Indian Med J* 2008; **57**: 293–7.
80. Clarke TR, Barrow G, Thompson D, Gibson R, Barton EN. Response to first line HAART using CD4 cell counts: experience in a university hospital in Kingston. *West Indian Med J* 2010; **59**: 439–44.
81. Barrow G, Clarke TR, Carrington D, Harvey K, Barton EN. An analysis of three opportunistic infections in an outpatient HIV clinic in Jamaica. *West Indian Med J* 2010; **59**: 393–9.